

Click, Zoom, Explore: Interactive 3D (*i*-3D) Figures in Standard Manuscript PDFs

Sourav Chatterjee,¹ Sooyeon Moon,^{1,2} Amanda Rowlands,³ Fred Chin,³ Peter H. Seeberger,^{1,2}
Nabyl Merbouh,*³ Kerry Gilmore*¹

- 1) *Department of Biomolecular Systems, Max-Planck-Institute of Colloids and Interfaces, Am Mühlenberg 1, 14476 Potsdam, Germany*
- 2) *Freie Universität Berlin, Institute of Chemistry and Biochemistry, Arnimallee 22, 14195 Berlin, Germany*
- 3) *Department of Chemistry, Simon Fraser University, 8888 University Drive, Burnaby, B.C., Canada V5A 1S6*

Abstract:

While chemistry exists in three-dimensions, it is published in two. This down-conversion results in a significant loss in information and often necessitates multiple images/figures to convey the complexity, intricacy, and beauty of a given structure. Outlined herein is a concise, straightforward method for incorporating interactive three-dimensional (*i*-3D) figures into manuscript pdfs. These figures can be generated from a variety of sources and allow for structures, molecular orbitals, unit cells and crystal lattices, as well as biopolymers to be published in the same information rich format as they are created and studied on our computers. These images can be seen and interacted with by anyone reading the manuscript in the standard pdf software (Adobe Reader) – and to fully appreciate this article, please read it using Adobe Reader. It is time for chemistry publications to take advantage of the digital age.

Sixty years ago, the first three-dimensional model of a protein (myoglobin) was created from X-Ray data.¹ This 3D model was then converted to a series of 2D images for publication to showcase the various viewpoints. Since this time, our ability to create and explore molecules in three-dimensions has significantly improved, allowing for the creation of beautiful representations users can manipulate on their computer. However, while image quality has improved, the scientific community is still limited by publishing their results as static, 2D images. This down-conversion represents the biggest obstacle in clearly conveying complex chemical information – three-dimensional structures, complexes, and interactions – in publications.

The depth of chemical knowledge which was possible to convey significantly improved with the development of chemical drawing programs like ChemDraw,² where complex structures, stereochemistry, non-bonding interactions, and molecular orbitals could all be drawn in a standardized format and easily incorporated into scientific papers. However, the representations of these complex structures are chosen by the authors, and often multiple images are required to fully convey the intended depiction³ – whether the favorable/unfavorable interactions of transition states or the different axes of crystal lattices (see SI). Even with multiple images, a significant loss of information must be accepted when publishing chemical/biological structures and complexes.

To date, there are few options for authors to transfer three-dimensional information to a reader. Figures can be published in stereo, creating a 3D image of a single viewpoint – if readers are capable of performing the visualization tricks necessary for seeing stereo images (Figure 1a),⁴ or as 2D images with QR codes for augmented reality viewing on a smartphone (Figure 1b).⁵

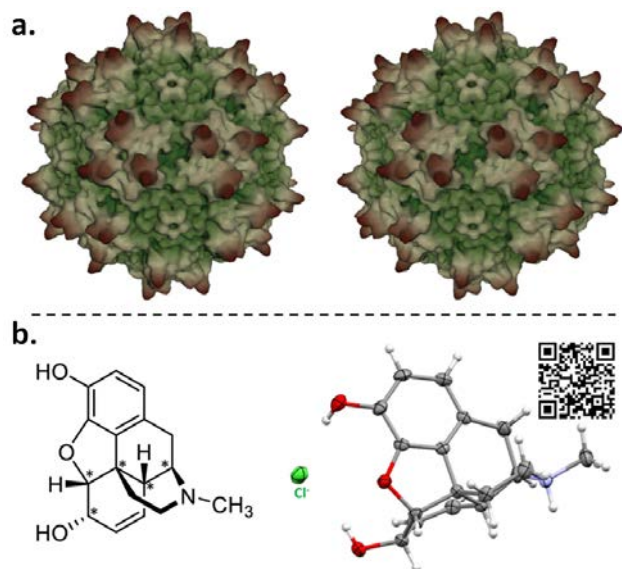


Figure 1: Representative examples of current methods for conveying three-dimensional molecular information in the literature. a) Stereo pair of outer surface of adeno-associated virus-2, reconstructed from 3D electron microscope image at 7.8 Å resolution. Reproduced with permission from ref 4. b) The Chemdraw and Ortep depictions of morphine and morphine hydrochloride,⁶ respectively, with QR code for direct link to 3D augmented reality interactive viewing using a smartphone app. Reproduced with permission from ref 5.

The dimensionality was limited as manuscripts were printed and bound in physical journals. Today, the vast majority of manuscripts are read on computers or mobile devices.⁷ Since 2004, Adobe Reader – the freely available program generally utilized for creating and viewing pdfs – has included the option for incorporation of 3D objects, and 3D images have been embedded in the text of biological⁸ and medical⁹ journals, as well as in supporting documents.^{10,11} Custom software toolboxes enable the ready generation of the files necessary to incorporate into publications.¹²

Several calls have been made for an easy, straightforward method for incorporating three-dimensional structures into published pdfs, for both scholarly^{13,14} and academic¹¹ purposes. Even though 3D pdfs would be exceedingly useful for chemists, they are almost entirely absent from the chemical sciences.

Here, we present concise, straightforward methods to incorporate three-dimensional structures of small molecules, molecular orbitals, complexes, crystal structures, and biopolymers into manuscript pdfs for publication. These 3D figures are fully interactive, allowing for rotation in all directions and zooming. The easy, stepwise process requires no more computer expertise than opening and saving files and the same manipulation techniques used in common drawing/visualization programs used in chemistry, biochemistry, and molecular biology laboratories.

The key file type (.u3d) which is embedded into the final manuscript pdf can be generated in two steps from a wide variety of file formats, including SMILES, xyz coordinates, .out, .fchk, .cif, and .pdb files (Figure 2). These file formats are converted to .wrl files using a variety of freeware or commercially available programs. Detailed, step-by-step instructions are provided in the supporting information, along with a series of examples, video tutorials, and tips for tricky functionalities/compounds. The .wrl file is then converted to .u3d file using an inexpensive, commercially available program called PDF3D,¹⁵ and is capable of rendering a wide variety of chemically relevant images including structures, molecular orbitals, and ribbon diagrams of

proteins. As seen with this manuscript, many complex 3D images relevant to the chemical sciences can be embedded into a single manuscript pdf without a prohibitive increase in file size.

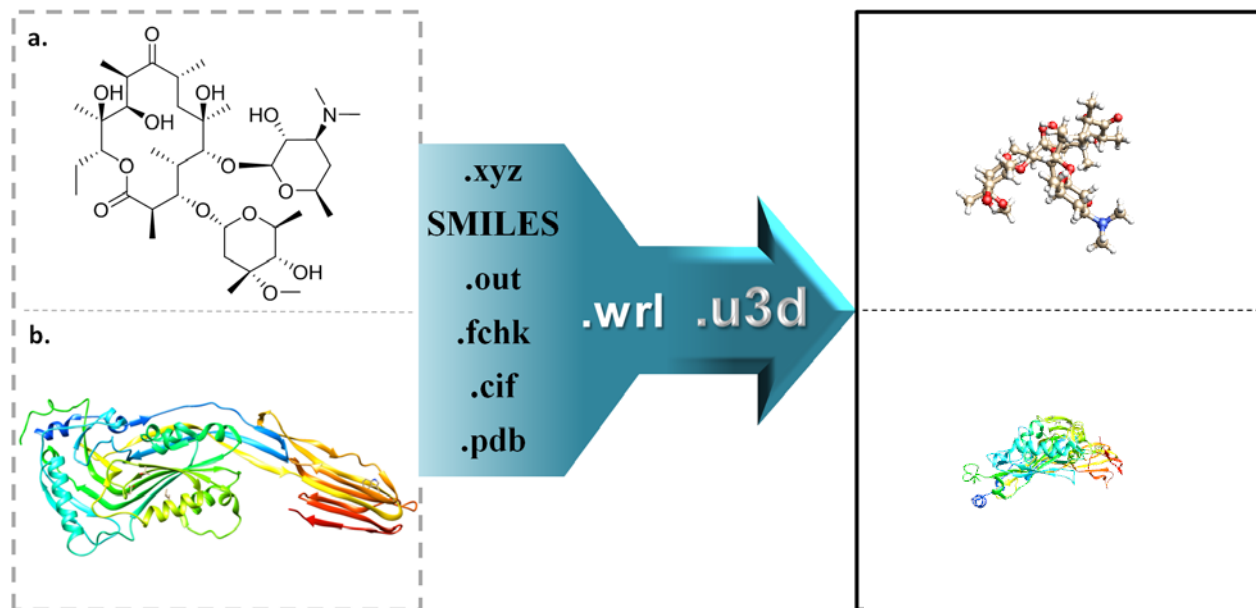


Figure 2: The respective workflows for creating interactive 3D images (black boxes) from a variety of file formats that can directly be embedded into pdf documents. Detailed instructions and tutorials for each category are available in the supporting information. In Adobe Reader, click to interact with the *i*-3D figures (black boxes, right). a) Erythromycin (antibiotic). b) Cytotoxin protein suliyisin from *Streptococcus suis*, reproduced with permission from ref 16. Color code: C: Gold, H: White, O: Red, N: Blue.

Three key pieces of molecular information are difficult to convey in two-dimensions: conformation, chirality/symmetry, and complexity. The conformation of a molecule is critical to understanding its stability and reactivity, and flat depictions belie the shape and orientation of a molecule (Figure 2a, SI). This is particularly true for molecular orbitals and transition states, where the ability to rotate, zoom, and explore a molecule's or complex's geometry provides a degree of clarity lost in a two-dimensional format (Figure 3a,b). Rendering can be changed by the reader to fully exploit a figure using the popup toolbar of the figure, for example changing the rendering mode from solid to shaded wireframe to see the boron-boron triple bond in Figure 3b. Similarly, depth is challenging to represent in 2D. With the ability to view a molecule from whichever direction the reader chooses, and then seamlessly expand the molecule, concepts such as molecular grooves, cavities, and chirality can be more easily comprehended and appreciated in published manuscripts with interactive 3D (*i*-3D) figures (Figure 3c).

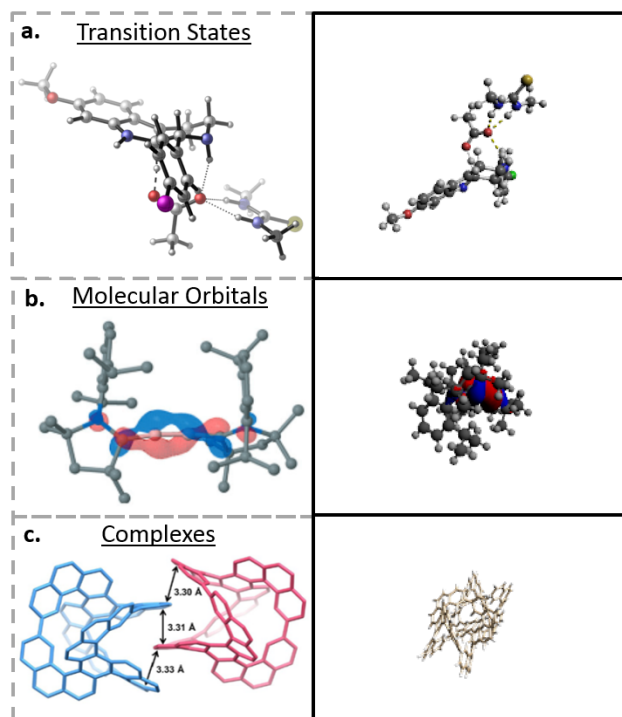


Figure 3: Representative examples of small molecules exemplifying the increase in both the degree and quality of information that can be conveyed in three-dimensions (right, black box) as opposed to two (left, grey dashed box). In Adobe Reader, click to interact with the *i*-3D figures. a) A transition state ((*S,R*)-TS₃•OAc•**1f**) of a chiral thiourea-catalyzed enantioselective Pictet-Spengler cyclization (B3LYP-D3(BJ)/6-31+G(d,p)/CPCM(toluene) level of theory), with dashed lines representing H-bonds, reproduced with permission from ref. 17. b) The LUMO orbitals of a CAAC-stabilized linear diboracumulene (CAAC)₂B₂, modified and reproduced with permission from ref 18. c) Crystal packing of a triple-helicene cage, with enantiomers shown in blue and pink. Solvent molecules omitted for clarity and the figure is reproduced with permission from ref 19. Color code for 3a: C: Dark grey, H: White, O: Red, N: Blue, Cl: Green (2D image: Pink), S: Yellow. Color code for 3b C: Dark grey, H: White, B: Pink.

This method is broadly applicable, providing the opportunity to significantly enhance how complicated chemical and biological information is conveyed in published work. Where this technique truly excels is in situations where multiple viewpoints are desired. Traditionally, multiple views (*i.e.* top, side) are required to convey an intended message/finding. The ability to allow the reader to rotate a molecule, complex, crystal lattice, or biopolymer increases the degree of potential understanding of the reader while minimizing space utilized on the page. Several representative examples (Figure 4) showcase how the orientation and alignment of small molecules (Figure 4a,b), complexes (Figure 4c), and crystals (Figure 4d) can be presented in a more rich format when accompanied, or solely, by the respective *i*-3D image.

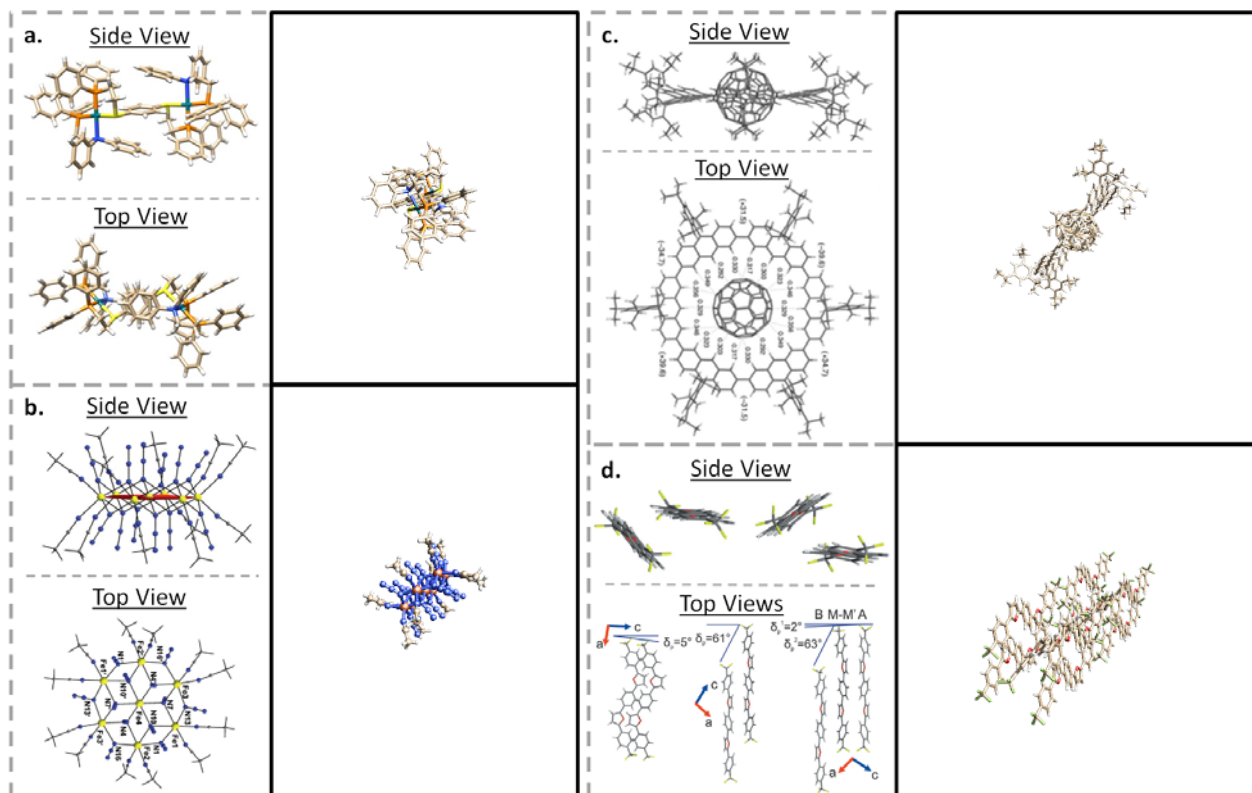


Figure 4: Representative examples of complex structures showcasing the advantages of being able to explore multiple viewpoints in an interactive format, depicted in their published two- (left, grey dashed boxes) and the *i*-3D versions (right, black boxes). In Adobe Reader, click to interact with the *i*-3D figures. a) The closed form of a triple-layer rhodium-based catalyst with views from the side and top, recreated from ref 20. Hydrogen atoms, solvent molecules, and counter ions omitted for clarity. b) A disk-like single-molecule magnet ($[\text{Fe}_7^{\text{II}}(\text{N}_3)_{12}(\text{MeCN})_{12}](\text{ClO}_4)_2$), reproduced with permission from ref 21. c) A host-guest complex of an anthracene cyclic ring and C_{60} (Nano-Saturn), reproduced with permission from ref 22. d) Crystal packing of a furan/phenylene co-oligomer single crystal (1,4-bis{5-[4-(trifluoromethyl)phenyl]furan-2-yl}benzene), reproduced with permission from ref 23. Color code for Figures 4a,4c and 4d: C: Gold, H: White, O: red, S: Yellow, N: Blue, P: Orange, Rh: Turquoise, F: Green. Color code for Figure 4b: C: Gold, H: White, N: Blue, Fe: Orange.

The ability to zoom into a figure allows the reader to gain significant clarity not just for large/complex molecules, but also for crystal structures and metal-organic frameworks, where both the unit cell/repeating unit and the crystal lattice can be shown in the same figure and along any axis desired (Figure 5a,b). A single *i*-3D image of a microporous MOF can showcase the pronounced Jahn-Teller distortion of the trans-oriented DMF molecules on the copper, the one-dimensional alignment of the Cu^{2+} ions, as well as the wide, rhombic channels of the layers (Figure 5a).²⁴

The ability to zoom in and out of supramolecular cages allows for the comprehension and examination of the contained space without the necessity of the author(s) depicting it with space filling shapes, which block the back side of the cage. This can be appreciated both with the empty $\text{M}_{12}\text{L}_{24}$ polyhedra “molecular flask”,²⁵ allowing readers to zoom into and explore the cavity (Figure 5c), and a neutral tetrahedron cage encapsulating a benzene molecule (Figure 5d).²⁶

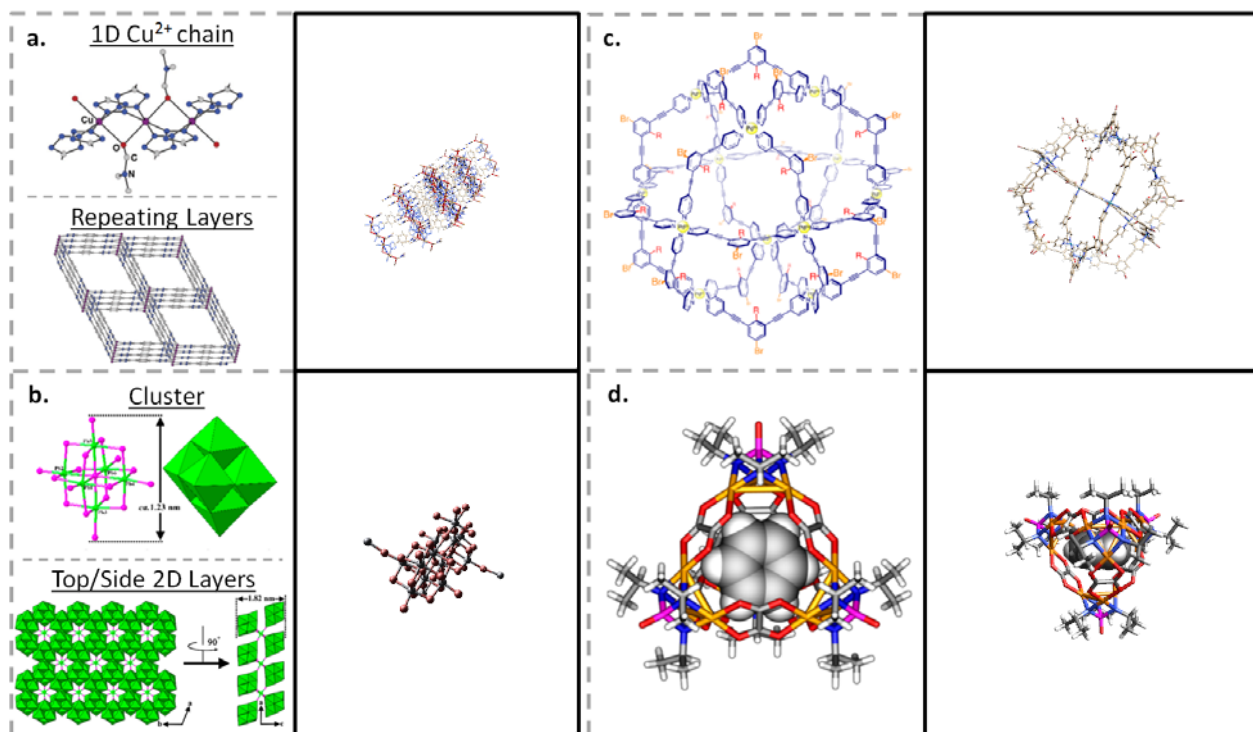


Figure 5: Representative examples where the ability to zoom increases the understanding conveyed and allows for exploration of the complexes depicted, shown here in their published two- (left, grey dashed boxes) and the *i*-3D versions (right, black boxes). In Adobe Reader, click to interact with the *i*-3D figures. a) Selected portions of the crystal structure of a copper-complex showing the copper (purple spheres) chain and layers. Hydrogen atoms and solvent molecules omitted for clarity, reproduced with permission from ref 24. b) The published side and top views of a 2D perovskite based on Lindqvist-type $[\text{Pb}_6\text{Br}_{19}]_7$ nanoclusters, recreated from ref 27. c) Solid-state structure of the supramolecular cage comprised of $\text{Pd}_{12}\text{L}_{124}\cdot 24\text{BF}_4$, with counterions and disordered sites omitted for clarity. Figure reproduced with permission from ref 25. d) A benzene molecule encapsulated within a charge-neutral tetrahedral cage, reproduced with permission from ref 26. Color code for Figure 5a and 5c: C: Gold, H: White, O: red, N: Blue, Cu: Orange, Pd: Turquoise. Color code for Figure 5b: Br: Red, Pb: Black. Color code for Figure 5d: C: black, H: White, O: Red, N: Blue, P: Pink, Pd: Orange.

Visualizing the intricacies of biopolymers has long been the target of publishing *i*-3D figures.¹⁴ Here, the ability to interact with the figure is paramount to understand and appreciate the complexity of these large molecules/complexes. The restricted 2D publishing format forces authors to utilize significant space to convey all the intricacies of their research. A representative example is the crystal structure of a Y-family DNA polymerase in action.²⁸ Only a selection of the figures the authors utilized to depict this crystal structure are shown in Figure 6. The different axial viewpoints, the different zoom depths, and the intricacies of the active site can fully be explored and conveyed in a single *i*-3D figure.

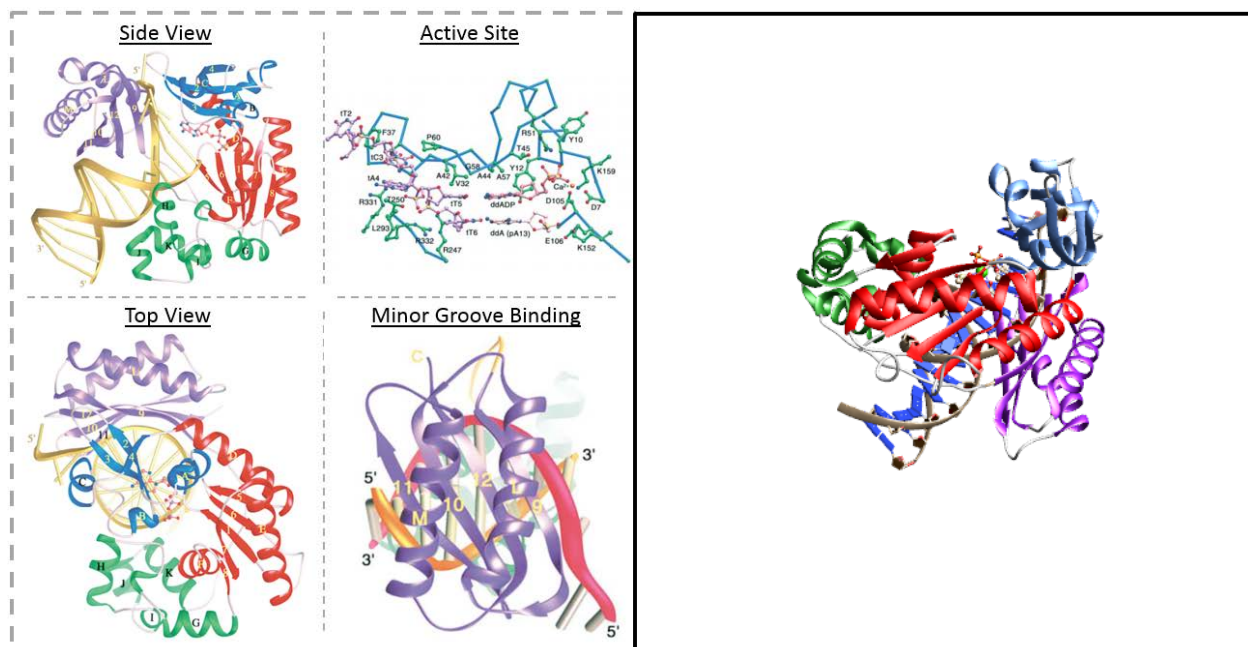


Figure 6: A representative example of the multiple viewpoints and zoom depths necessary to convey the complexity of biopolymers and biological complexes, such as the Y-family DNA polymerase complexed to a piece of double-stranded DNA. The published 2D (left, grey dashed boxes) figures are reproduced with permission from ref 28. The single *i*-3D version is shown to the right (black box). In Adobe Reader, click to interact with the *i*-3D image. Color code: C: Gold, H: White, Oxygen: Red, S: Yellow, N: Blue, P: Orange, Ca: Green

In 1958, the first three-dimensional structure was obtained from a crystal structure¹ and depicted by multiple viewpoints to display all sides of this iron- and oxygen-binding protein. This seminal work is compared to the interactive three-dimensional representation in Figure 7.

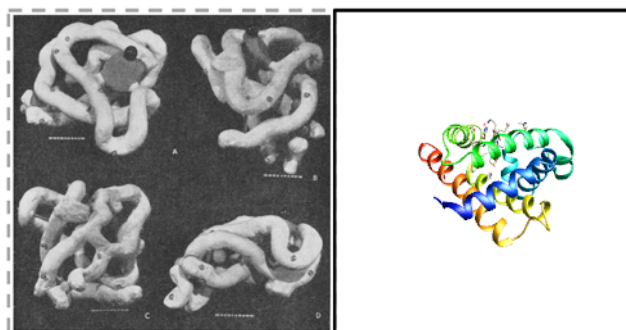


Figure 7: (Left) The original figure depicting the multiple viewpoints of myoglobin, reproduced with permission from ref 1. (Right) The *i*-3D image of same crystal structure, solvent molecules omitted for clarity. In Adobe Reader, click to interact with the *i*-3D image. Color code: C: Gold, Oxygen: Red, N: Blue, Fe: Orange.

In conclusion, molecules are three-dimensional, and the ability to depict the intricacies, complexities, and orientations of structures and complexes is paramount to successfully convey findings in publications. While authors have traditionally been restricted to creating static two-dimensional figures, the shift from print to online publication allows authors to create and publish interactive, information-rich three-dimensional figures – complementing or replacing traditional representations. Interactive 3D figures save space and increase the worth of figures depicting chemical structures/complexes/interactions. The process to incorporate these figures into

manuscript pdfs is concise and straightforward and is outlined in detail in the supporting documents and videos. It is time for chemistry publications to take advantage of the digital age.

Acknowledgements:

The authors would like to thank the Simon Fraser University Chemistry Department, the Max-Planck Society, and DFG InChEM (FOR 2177) for the generous financial support.

Corresponding Authors:

Nabyl Merbouh (nabyl_merbouh@sfu.ca)

Kerry Gilmore (kerry.gilmore@mpikg.mpg.de)

Supporting Information:

Detailed procedures and tutorials for the generation of .u3d files from a variety of sources, and for their incorporation into manuscript pdfs. Troubleshooting is also provided for all functional groups and compounds identified in the course of this work that required additional steps. Video tutorials showing the steps of conversion are provided. Additional examples of all classes of organic, organometallic, inorganic, and biological compounds are provided.

References:

-
- ¹ (a) Kendrew, J. C.; Bodo, G.; Dintzis, H. M.; Parrish, R. G.; Wyckoff, H.; Phillips, D. C. A three-dimensional model of the myoglobin molecule obtained by x-ray analysis. *Nature* **1958**, *181*, 662-666. (b) Kendrew, J. C.; Dickerson, R. E.; Strandberg, B. E.; Hart, R. G.; Davies, Phillips, D. C.; Shore, V. C. Structure of Myoglobin: A Three-Dimensional Fourier Synthesis at 2 Å. Resolution. *Nature* **1960**, *185*, 422-427.
 - ² Evans, D. A. History of the Harvard ChemDraw project. *Angew. Chem. Int. Ed.* **2014**, *53*, 11140-11145.
 - ³ Tory, M.; Möller, T. Human factors in visualization research. *IEEE Trans. Vis. Comput. Graph.* **2004**, *10*, 72-84.
 - ⁴ O'Donnell, J.; Taylor, K. A.; Chapman, M. S. Adeno-associated virus-2 and its primary cellular receptor-Cryo-EM structure of a heparin complex. *Virology* **2009**, *385*, 434-443.
 - ⁵ Wolle, P.; Müller, M. P.; Rauh, D. Augmented Reality in Scientific Publications-Taking the Visualization of 3D Structures to the Next Level. *ACS Chem. Biol.* **2018**, *13*, 496-499. Example program for viewing image: Augment (Android), accessed November 20, 2018.
 - ⁶ Gelbrich, T.; Braun, D. E.; Griesser, U. J. Morphine hydro-chloride anhydrate. *Acta Cryst.* **2012**, *E68*, o3358-o3359.
 - ⁷ Vaughan, K. T. L. Changing use patterns of print journals in the digital age: Impacts of electronic equivalents on print chemistry journal use. *J. Am. Soc. Inf. Sci. Tec.* **2003**, *54*, 1149-1152.
 - ⁸ Ruthensteiner, B.; Heß, M. Embedding 3D Models of Biological Specimens in PDF Publications. *Microsc. Res. Techniq.* **2008**, *71*, 778-786.
 - ⁹ (a) Ziegler, A.; Mietchen, D.; Faber, C.; von Hausen, W.; Schöbel, C.; Sellerer, M.; Ziegler, A. Effectively incorporating selected multimedia content into medical publications. *BMC Med.* **2011**, *9*, 17. (b) Danz, J. C.; Katsaros, C. Three-dimensional portable document format: A simple way to present 3-dimensional data in an electronic publication. *Am. J. Orthod. Dentofac. Orthop.* **2011**, *140*, 274-276.
 - ¹⁰ Barnes, D. G.; Vidiassov, M.; Ruthensteiner, B.; Fluke, C. J.; Quayle, M. R.; McHenry, C. R. Embedding and publishing interactive, 3-dimensional, scientific figures in Portable Document Format (PDF) files. *PLoS One* **2013**, *8*, e69446.
 - ¹¹ (a) Cody, J. A.; Craig, P. A.; Loudermilk, A. D.; Yacci, P. M.; Frisco, S. L.; Milillo, J. R. Design and implementation of a self-directed stereochemistry lesson using embedded virtual three-dimensional images in a portable document format. *J. Chem. Educ.* **2012**, *89*, 29-33. (b) Günersel, A. B.; Fleming, S. A. Qualitative assessment of a 3D simulation program: Faculty, students, and bio-organic reaction animations. *J. Chem. Educ.* **2013**, *90*, 988-994.

- ¹² (a) Neue, A. Enriching scientific publications with interactive 3D PDF: an integrated toolbox for creating ready-to-publish figures. *PeerJ Comput. Sci.* **2016**, *2*, e64. (b) Neue, A. Towards an easier creation of three-dimensional data for embedding into scholarly 3D PDF (Portable Document Format) files. *PeerJ* **2015**, *3*, e794.
- ¹³ (a) Murienne, J.; Ziegler, A.; Ruthensteiner, B. A 3D revolution in communicating science. *Nature* **2008**, *453*, 450. (b) Vasilyev, V. Towards interactive 3D graphics in chemistry publications. *Theor. Chem. Acc.* **2010**, *125*, 173-176. (c) Tyzack, J. K. Dragging (and zooming and rotating) publication of 3D molecular structures into the 21st century. *Trends Biochem. Sci.* **2008**, *33*, 405-407.
- ¹⁴ (a) Kumar, P.; Ziegler, A.; Ziegler, J.; Uchanska-Ziegler, B.; Ziegler, A. Grasping molecular structures through publication-integrated 3D models. *Trends Biochem. Sci.* **2008**, *33*, 408-412. (b) Kumar, P.; Ziegler, A.; Grahn, A.; Hee, C. S.; Ziegler, A. Leaving the structural ivory tower, assisted by interactive 3D PDF. *Trends Biochem. Sci.* **2010**, *35*, 419-422.
- ¹⁵ <https://www.pdf3d.com>, visited December 6th, 2018.
- ¹⁶ Xu, L.; Huang, B.; Du, H.; Zhang, X. C.; Xu, J.; Li, X.; Rao, Z. Crystal structure of cytotoxin protein suliyisin from *Streptococcus suis*. *Protein Cell* **2010**, *1*, 96-105.
- ¹⁷ Klausen, R. S.; Kennedy, C. R.; Hyde, A. M.; Jacobsen, E. N. Chiral Thioureas Promote Enantioselective Pictet-Spengler Cyclization by Stabilizing Every Intermediate and Transition State in the Carboxylic Acid-Catalyzed Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 12299-12309.
- ¹⁸ Böhnke, J.; Braunschweig, H.; Ewing, W. C.; Hörl, C.; Kramer, T.; Krummenacher, I.; Mies, J.; Vargas, A. Diborabutatriene: An Electron-Deficient Cumulene. *Angew. Chem. Int. Ed.* **2014**, *53*, 9082-9085.
- ¹⁹ Matsushima, T.; Kikkawa, S.; Azumaya, I.; Watanabe, S. Triple Helicene Cage: Three-Dimensional π -Conjugated Chiral Cage with Six [5] Helicene Units. *ChemistryOpen* **2018**, *7*, 278-281.
- ²⁰ Yoon, H. J.; Kuwabara, J.; Kim, J.-H.; Mirkin, C. A. Allosteric supramolecular triple-layer catalysts. *Science* **2010**, *330*, 66-69.
- ²¹ Alexandropoulos, D. I.; Vignesh, K. R.; Stamatatos, T. C.; Dunbar, K. R. Rare "Janus"-Faced $\{\text{Fe}^{\text{II}}_7\}$ Single-Molecule Magnet Exhibiting Intramolecular Ferromagnetic Interactions. *Chem. Sci.* **2019**, DOI: 10.1039/c8sc04384a.
- ²² Yamamoto, Y.; Tsurumaki, E.; Wakamatsu, K.; Toyota, S. Nano-Saturn: Experimental Evidence of Complex Formation of an Anthracene Cyclic Ring with C_{60} . *Angew. Chem. Int. Ed.* **2018**, *57*, 8199-8202.
- ²³ Sonina, A. A.; Koskin, I. P.; Sherin, P. S.; Rybalova, T. V.; Shundrina, I. K.; Mostovich, E. A.; Kazantsev, M. S. Crystal packing control of a tri-fluoro-methyl-substituted furan/phenylene co-oligomer. *Acta Cryst.* **2018**, *B74*, 450-457.
- ²⁴ (a) Dincă, M.; Yu, A. F.; Long, J. R. Microporous Metal-Organic Frameworks Incorporating 1,4-Benzeneditetrazolate: Syntheses, Structures, and Hydrogen Storage Properties. *J. Am. Chem. Soc.* **2006**, *128*, 8904-8913. (b) Dincă, M.; Yu, A. F.; Long, J. R. Microporous Metal-Organic Frameworks Incorporating 1,4-Benzeneditetrazolate: Syntheses, Structures, and Hydrogen Storage Properties [J. Am. Chem. Soc. 2006, 128, 8904-8913]. *J. Am. Chem. Soc.* **2006**, *128*, 17153-17153.
- ²⁵ Bruns, C. J.; Fujita, D.; Hoshino, M.; Sato, S.; Stoddart, J. F.; Fujita, M. Emergent Ion-Gated Binding of Cationic Host-Guest Complexes within Cationic $\text{M}_{12}\text{L}_{24}$ Molecular Flasks. *J. Am. Chem. Soc.* **2014**, *136*, 12027-12034.
- ²⁶ Gupta, A. K.; Yadav, A.; Srivastava, A. K.; Ramya, K. R.; Paithankar, H.; Nandi, S.; Chugh, J.; Boomishankar, R. A Neutral Cluster Cage with a Tetrahedral $[\text{Pd}_{12}^{\text{II}}\text{L}_6]$ Framework: Crystal Structures and Host-Guest Studies. *Inorg. Chem.* **2015**, *54*, 3196-3202.
- ²⁷ Li, X.; Do, T. T. H.; del Águila, A. G.; Huang, Y.; Chen, W.; Li, Y.; Ganguly, R.; Morris, S.; Xiong, Q.; Li, D.-s.; Zhang, Q. Two-Dimensional and Emission-Tunable: An Unusual Perovskite Constructed from Lindqvist-Type $[\text{Pb}_6\text{Br}_{19}]^{7-}$ Nanoclusters. *Inorg. Chem.* **2018**, *57*, 14035-14038.
- ²⁸ Ling, H.; Boudsocq, F.; Woodgate, R.; Yang, W. Crystal structure of a Y-family DNA polymerase in action: a mechanism for error-prone and lesion-bypass replication. *Cell* **2001**, *107*, 91-102.